Reduced-intensity conditioning for allogeneic stem cell transplantation in patients with chronic myeloid leukemia is associated with better overall survival but inferior disease-free survival when compared with myeloablative conditioning – a retrospective study of the Czech National Hematopoietic Stem Cell Transplantation Registry

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Received January 10, 2007

Allogeneic stem cell transplantation (AlloSCT) has been currently recommended in the treatment of patients with chronic myeloid leukemia (CML) as a second option after imatinib failure or in selected group of patients with high-risk CML and low risk for transplant-related mortality. The actual role of reduced-intensity conditioning (RIC) before AlloSCT in CML patients has not been yet conclusively established. The Czech National Hematopoietic Stem Cell Transplantation Registry has conducted a retrospective analysis of all patients (n=29) transplanted after RIC from the Registry database containing 295 patients with CML transplanted in the Czech Republic in years 1988-2005 and compared them with patients at comparable age (median age 48.3 and 50.6 years, respectively; p=0.587) transplanted during the same period of time using conventional myeloablative conditioning (n=26). Survival advantage of patients transplanted after RIC has been confirmed by log rank test (p=0.036) despite the fact that the relapse rate was significantly higher in RIC group (44.8% versus 0%). Both groups did not differ significantly in the use of voluntary unrelated donors, type of the grafts and in incidence of acute graft versus host disease (GVHD). However, there were trends for higher risk of CML and higher use of unrelated donors in the myeloablative group while peripheral stem cell grafts and chronic GVHD were observed more frequently in the RIC group. Transplant-related mortality was the leading cause of death in both groups of patients. Our results should be interpreted with caution because they may be influenced by small groups of subjects and also the impact of patients with high EBMT risk score on inferior survival in the myeloablative group cannot be fully eliminated. More retrospective and prospective studies are needed to elucidate the actual role of RIC before AlloSCT for CML.

Key words: allogeneic stem cell transplantation, chronic myeloid leukemia, reduced-intensity conditioning, imatinib

The introduction of imatinib into the treatment of chronic myeloid leukemia (CML) has resulted not only in a rapid decline in the rate of allogeneic stem cell transplantation (AlloSCT) for CML in Europe [1] but, subsequently, has necessitated the revision of recommendations for CML treatment [2]. According to the recently issued statement of the European LeukemiaNet expert panel imatinib is generally preferred to AlloSCT for the initial treatment. The high treatment-related mortality during early years after the procedure has remained as the leading problem of AlloSCT resulting in long-term survival of 53% of patients transplanted in early chronic phase using HLA identical sibling [3]. Reduced-intensity conditioning (RIC) has been currently evaluated as an option for reduction of transplant-related mortality and as an approach enabling AlloSCT in older and co-morbid patients. Despite early optimistic reports [4] recent EBMT multi-center retrospective study has shown only 58% probability of overall

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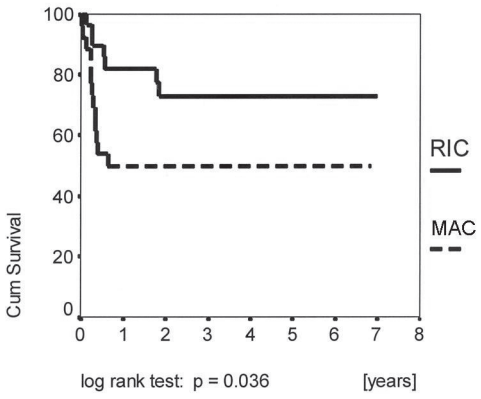

Figure 1. The comparison of cumulative survival of patients with CML transplanted after reduced-intensity conditioning (RIC) and myeloablative conditioning (MAC). The significance of the difference was confirmed by log rank test.

survival at 3 years and 23.3% transplant-related mortality at 2 years [5]. The European LeukemiaNet expert panel has not issued any recommendations for the use of RIC in CML because the long-term impact of this procedure cannot be assessed yet [2].

The Czech National Hematopoietic Stem Cell Transplantation Registry in co-operation with the Transplant Center at Pilsen has recently undertaken a retrospective evaluation of the results of AlloSCT for CML in the Czech Republic [6]. We report here a retrospective study aimed to assess the results of RIC and compare them with the results of AlloSCT after myeloablative conditioning used in the patients of comparable age.

Patients and methods

All data have been retrieved from the EBMT Promise database under supervision of data managers of the Czech National Hematopoietic Stem Cell Transplantation Registry and the Pilsen transplantation center. All data were checked-up and updated. From all patients with CML after AlloSCT transplanted at six centers in the Czech Republic in years 1988-2005 patients transplanted with the use of RIC without the use of total body irradiation were selected as the study group. From the same database control group of patients with CML at comparable age transplanted using conventional conditioning (with or without total body irradiation) during the same period was chosen. Both groups were compared with respect to age, risk of CML, EBMT risk score, type of donor, type of graft, incidence of graft versus host disease (GVHD), overall survival, incidence of relapse and transplant-related complications. For statistical analysis chi-square test, t-test and log rank test were used. Because of the retrospective fashion of the study no uniform protocols for prevention and treatment of transplant-related complication (GVHD and infections) were used and the data on the actual prevention and treatment of transplant-related complication were not compared. Also there were no common protocols for monitoring of patients after transplantation and treatment of relapse after AlloSCT. According to the registry data both donor lymphocyte infusions and imatinib therapy were used according to the individual center decision.

Results

295 patients with CML were transplanted using sibling, other relative or voluntary unrelated donor at six centers in the Czech Republic in years 1988-2005. For the purpose of this study, 29 patients were identified who were transplanted using RIC without the use of total body irradiation. These patients represented 9.8% of the total number of AlloSCT for CML in the Czech Republic. Median age of patients was 48.3 years (range 19.2-57.0). As RIC the combination of fludarabine and cyclophosphamide was used in one case, the combination of fludarabine, busulfan and anti-thymocyte globuline was used in remaining patients. The one patient prepared with fludarabine and cyclophosphamide has rejected the graft and has failed to respond to repeated donor lymphocyte infusions. He was treated with imatinib and achieved molecular response with negativity of BCR-ABL in nested RT-PCR. All other patients have engrafted. Control group consisted of 26 patients at comparable age (range 15.1-59.5; median 50.6 years; p=0.587) transplanted after standard myeloablative conditioning during the same period. Details about patients are given in Table 1 including phase of disease, interval from the diagnosis to transplantation, EBMT risk score, period of observation, type of donor and graft and occurrence of GVHD and relapse. 7 (24%) patients died in the study group and 13 (50%) patients of the controls. Transplant-related complications (GVHD and infections) were the leading cause of mortality in both groups (in study group 5 and in control group 12 deaths, respectively). Only one patient in the study group died due to the relapse of CML. No relapse occurred in the control group while there were 13 relapses (6 of them hematologic) in the study group. For the treatment of relapse combination of imatinib and donor lymphocyte infusions were used according to the individual center protocols in all patients. Despite the high relapse risk in the study group this did not result in the increase of mortality. The probability of overall survival according Kaplan and Meier of both groups of patients was compared using log rank test which confirmed the significantly better overall survival in RIC (study) group (p=0.036; Figure 1).

Discussion

AlloSCT is the only available curative option for the therapy of CML [7]. However, due to the risk of transplant-related complications associated with considerable morbidity and mortality long-term survival of only 53% of patients trans-

Table 1 Patients' characteristics and outcome

Characteristic	Myeloablative conditioning (%)	RIC (%)	P value	Test
n	26	29		
Sex				
Male	16 (61.5)	15 (51.7)		
Female	10 (38.5)	14 (48.3)	0.464	chi-square test
Age	48.3 (19-57)*	50.6 (15-59)*	0.587	t-test
Interval from DG to SCT (days)	334.5 (82-3314)*	305 (82-6511)*	0.239	t-test
CML phase				
1.CP	19 (73.1)	24 (82.8)		
2.CP	1 (3.9)	3 (10.4)		
AP	3 (11.5)	1 (3.4)		
BP	3 (11.5)	1 (3.4)	0.188	chi-square test
Donor				
HLA identical sibling	14 (53.9)	22 (75.9)		
VUD	10 (28.4)	5 (17.2)		
Other	2 (7.7)	2 (6.8)	0.193	chi-square test
Source of the graft				
Bone marrow	8 (30.8)	5 (17.2)		
Peripheral stem cells	18 (69.2)	24 (82.8)	0.238	chi-square test
EBMT risk score				
0 – 2	6 (23.1)	12 (41.3)		
3 – 4	15 (57.7)	15 (51.7)		
5 – 6	5 (19.2)	2 (6.9)	0.139	chi-square test
Overall survival (days)	257 (7-2499)*	737 (49-2543)*	0.035	log-rank test
Acute GVHD				
absent	9 (34.6)	14 (48.3)		
grade II-IV	11 (42.3)	9 (31)	0.298	chi-square test
Chronic GVHD	6 (23)	12 (41.4)	0.148	chi-square test
Relapse	0	13 (44.8)	0.0003	chi-square test with Yates correction
Molecular		4 (13.8)		
Cytogenetic		3 (10.3)		
Hematologic		6 (20.7)		

Legend: * = median (range); DG = diagnosis; SCT = stem cell transplantation; CP = chronic phase; AP = accellerated phase; BP = blastic phase; VUD = voluntary unrelated donor.

planted in early chronic phase using HLA identical sibling has been reported [3]. AlloSCT has been currently recommended in the treatment of patients with CML as a second option after imatinib failure or in selected group of patients with high-risk CML and low risk for transplant-related mortality [2]. The strategies for improvement of AlloSCT results include introduction of RIC that has been currently evaluated as an option for reduction of transplant-related mortality and as an approach enabling AlloSCT in older and co-morbid patients. However, the actual role of RIC before AlloSCT in CML patients has not been conclusively established. Despite early optimistic reports [4] recent EBMT multi-center retrospective study has shown only 58% probability of overall survival at 3 years and 23.3% transplant-related mortality at 2 years [5]. In this study almost identical risk of CML relapse (47%) after transplantation was reported as we have observed in our analysis. No retrospective comparative studies or prospective studies evaluating the role of RIC in AlloSCT for CML have been reported until today.

Our study was undertaken with the aim to compare RIC with myeloablative conditioning in patients with CML at comparable age. Data from EBMT Promise registry were used for a retrospective study. Limitations of such an analysis include lack of the common protocols for management

of patients. Despite the fact that our groups of patients were relatively homogenous with respect to the conditioning, strategies used in prevention and treatment of transplant-related complications and relapse were center-dependent. Therefore, these parameters were not analyzed in detail. In addition, the final numbers of patients analyzed were relatively small to enable any conclusive results. Due to this the two groups may have not been fully comparable because there have been trends for the preference of myeloablative conditioning in patients with more advanced stage of CML and with higher EBMT score (Table 1). The other trend observed – the higher rate of chronic GVHD in the RIC group – was probably associated with the more frequent use of peripheral blood stem cell [8]. The most striking difference was observed in the relapse rate – 44.8% in RIC comparing to 0% in myeloablative group resulting in inferior disease-free survival but not in impairment of overall survival of the RIC group. This has reflected the well-known fact about high response rate of early-detected CML relapse after AlloSCT to the treatment with donor lymphocyte infusions and/or imatinib [9]. The reasons of such a marked difference in relapse rate may include not only reduced intensity of conditioning but also various risk of CML and various strategies in GVHD prophylaxis. Discussion of these problems is beyond the scope of this article. On the other hand, it is of interest that the overall survival of our study group patients was better than in the paper of Crawley and co-workers [5]. However, longer observation period may be needed to analyze conclusively responses of relapse treatment.

In conclusion, our registry-based retrospective analysis was performed in order to evaluate the role of RIC in AlloSCT in CML patients. Data of patients transplanted after RIC were compared with those of patients in whom myeloablative conditioning was used. We have shown the limitations of such a comparison. Results of our study should be interpreted with caution because the impact of the higher proportion of patients with high EBMT risk score in myeloablative group cannot be fully eliminated and both groups were too small and their follow-up was too short to allow any reliable conclusions. Retrospective comparisons based on larger databases or/and prospective controlled studies for evaluation of the role of RIC in CML are clearly needed.

The work was supported by the grant IGA MZ NR/8223-3.

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